However, Applicants respectfully note that a description by a function, such as of a cartilage and bone-inducing ability, is an acceptable method of describing a genus, particularly in view of the relevant references listed on pages 1-3 of the present specification.

Applicants respectfully submit that much was known about proteins of the TGF-β superfamily, about fusion proteins, heterodimers and the like containing such proteins already at the filing date of the present application. The sequences of MP52 were known and published as of the present filing date as well as those of many other proteins of the TGF-β family. It was already known from the prior art as well which parts of these proteins are especially important for biological activity and many fragments and protein parts had been published and contained in published patent applications, respectively, which at least essentially retain their biological activity.

For example, there is a substantial amount of literature concerning TGF-β heterodimers and activin heterodimers, e.g. U.S. Patent 4,931,548 concerning TGF-β heterodimers (cf. enclosed Abstract), U.S. Patent 5,462,925 concerning TGF-β 2/ 3 heterodimders (cf. enclosed Abstract); U.S. Patent 5,482,851 concerning, inter alia, TGF-β1/β 3 heterodimers (cf. enclosed Abstract) or U.S. Patent 5,413,989 (cf. enclosed Abstract) mentioning, inter alia, heterodimers of activin βAβB, EP O 626 451 describes the production of heterodimers of the TGF-β superfamily in insect cells. WO 92/08480 also describes heterodimers of TGF-β 2 and TGF-β 3. Furthermore, please note the article by Ogawa et al. and Cheifnitz et al. (cf. enclosed Abstract).

Applicants also note that there are heterodimers found under physiological conditions, as well as ones produced artificially. This can be gathered from the above-mentioned references. Thus, there is much knowledge in the art about heterodimers, and it is also known that they have bone- and/or cartilage-inducing potential. As of the filing date of the present application, thus, much had been known already among those of skill in the art. Regarding the fusion proteins it is

noted, for example, in the article by Hammonds et al. (cf. enclosed Abstract), it is shown that the proregion of BMP-2 can be fused with the mature region of BMP-4 and an increased amount of active BMP-4 is expressed.

Regarding the item as to which domains are sufficient for cartilage and bone formation, respectively, Applicants refer to the article by Sampath et al. (cf. enclosed Abstract). Fig.2B thereof shows various OP-1 proteins which lack varying numbers of amino acids at the N-terminus. On page 20357 it is stated that these "truncated forms" have the same activity as mature OP-1. However, these "truncated forms" are also mentioned in WO 91/05802 by Creative Biomolecules, which the Examiner cites in this application with regard to the collagen matrix. Pages 26 (3rd paragraph) to page 29 are of interest here. However, the 7 cysteine region is not mentioned therein, the shortest protein starts 12 amino acids before the 1st protein.

Regarding vertebrates, it is submitted that MP52 was strongly preserved during vertebrate evolution, as is typical for the members of the TGF-β family. In particular, mouse GDF-5 (GDF-5 and MP52 are used synonymously, U.S. 5,801,014) which in the mature part differs from human GDF-5/MP52 only by one arnino acid as well as GDF-5, from chicken (sequence, however, only known after the priority date of the present application) which in the mature part differs from human GDF-5MP52 only by 2 amino acids. Enclosed is an alignment (CLUSTAL W) of the three mature proteins. "*" indicates an identical amino acid in all three proteins.

Similarly to the above rejection, the Office Action also rejects claims 14-27 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification for an implant material containing fragments, portions, or heterodimers of members of the TGF-β superfamily, or non-human homologues of SEQ ID NO: 1. Applicants believe the issues in this rejection are substantially the same as in the above rejection of claims 15 and 16 and the above comments apply to this rejection also.

For at least the above reasons, reconsideration and withdrawal of the rejections of claims 15 and 16 and of claims 14-27 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

SECTION 103 REJECTION

The Office Action rejects claims 14-27 under 35 U.S.C. § 103(a) as being obvious over Urist et al. (U.S. Patent No. 4,596,574) in view of Opperman et al. (WO 91/05802) and Yan et al. This rejection is traversed.

Urist et al. and Opperman et al. were discussed in Applicants' February 9, 2000 Response. In particular, it was noted therein that neither reference taught a bioactive matrix.

In particular, as Applicants noted therein, Urist is directed to a delivery system for BMP comprising a composition of a physiologically acceptable, biodegradable porous ceramic containing substantially pure BMP which allows the BMP to be delivered on a sustained basis to bone tissue. The porous ceramic is preferably sintered calcium phosphate, preferably tricalcium phosphate, and especially preferably .-tricalcium phosphate. The pores of the ceramic are suitable for containing effective amounts of lyophilized BMP. The BMP-porous ceramic delivery system is prepared by introducing a physiologically acceptable biodegradable porous ceramic to an aqueous BMP solution and causing the BMP to become entrapped in the ceramic's pores by evaporating the solvent or freeze-drying it.

The present claims contain the limitation that the matrix material is "bioactive". The matrix according to Urist is not bioactive. This is clearly indicated by the Example on column 4, line 57 through column 5, line 51. In this example, BMP is implanted on β-tricalcium phosphate and, as a control, β-tricalcium phosphate having no BMP thereon is implanted in muscle pockets of mice. The implants are tested after several days. In the control test, which only contains the β-tricalcium phosphate matrix, no bone growth was detected (i.e.,

there is no "bioactivity"). Instead, the negative side effects of the implant, such as infectious reactions, infiltration of macrophages and multinuclear giant cells and encapsulation in fibrous connective tissue) are described. All of these side effects can be avoided by the matrix of the present invention. Applicants refer the Examiner to page 13, end of the first paragraph, of the present specification. In order to avoid the side effects experienced using the Urist matrix, it is important to achieve a corresponding crystallographic phase purity (see page 7, first paragraph, of the present specification). Consequently, the matrices of the present application are decisively different from those of Urist.

Oppermann et al. is directed to an osteogenic device comprising matrices containing dispersed osteogenic protein produced from recombinant DNA and capable of bone induction in allogenic and xenogenic implants. The matrix in Oppermann comprises biocompatible, protein-extracted, mineral-free, dilapidated, insoluble Type-I bone collagen particles which may be allergenic or xenogenic to the host. The particle size of the matrix is within the range of 70-850 μm, and the matrix may be fabricated by close packing the particles into a shape spanning the bone defect.

It is clear that Oppermann contains no disclosure or suggestion whatsoever that the matrix material should be composed of a calcium phosphate, as claimed herein. In addition, as with Urist, it is clear that the matrix of Oppermann is not "bioactive", as required in the present invention. It is clearly disclosed in Oppermann that the matrix alone does not induce bone growth. See, for example, page 52, lines 13-14 and page 56, lines 14-16.

However, the Examiner has cited Yan et al. as disclosing that materials comprising predominantly tricalcium phosphate are bioactive. Applicants note that, while the Yan et al. abstract does appear to describe such a calcium phosphate that "can induce new bone growth," Applicants cannot find a suggestion in the applied references nor do Applicants believe that there would have been any motivation to combine MP52 with a matrix having a bone inducing

activity. Thus, Applicants do not believe that the presently claimed invention would have been obvious over the applied combination of references.

Furthermore, Applicants only have an Abstract of the Yan article, with the complete text apparently being in Chinese. However, based only on the Abstract, the Yan article contains no hint as to a possible combination with MP52 and such a combination was not suggested by combination with the other references either. The other references rather gave the impression that a combination of a bone-inducing factor with a non-bioactive matrix is desirable and favorable.

The Yan Abstract does not mention a combination with other factors stimulating bone growth and only states very generally that the matrix used therein allegedly can induce bone growth. However, no evidence thereof is furnished, at least not in the part that can be understood (the Abstract).

However, Applicants have previously explained that Applicants' combination of bone-inducing factor and bioactive matrix achieves an unexpected synergistic effect which is advantageous. None of the applied references teach or suggest that such a synergistic effect could be achieved.

For at least the above reasons, reconsideration and withdrawal of the rejections of claims 14-27 under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.